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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,796	04/19/2001	Heinz-Jurgen H.J. Thiel	2000.552 US	2897

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	14

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,796	THIEL ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 35-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the method of attenuating should be examined with the attenuated pestivirus. This is not found persuasive because the instant pestivirus can be attenuated by materially different means, such as serial passage and chemical treatment. The requirement is still deemed proper and is therefore made FINAL.

Claims 25-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Sequence Compliance

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification and the claims. Any sequence containing four or more amino acids and ten or more nucleotides must be identified with a SEQ ID NO. See 37 CFR § 1.821.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The disclosure is objected to because of the following informalities: the section labeled "Legends to the Figures" should be renamed "Brief Description of the Drawings" and should follow the "Background of the Invention" section.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 15 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The pestivirus mutant of claim 15 encompasses naturally occurring pestivirus mutants that have not been isolated. This rejection affects all dependent claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-24 and 35-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is unclear and confusing in terms of what is being mutated. The claim states that the attenuated pestivirus comprises one or more mutations in one or both stem loops Ia and Ib, wherein the 5' nucleotide sequence is GUAU. It is presumed that this 5' sequence is a naturally occurring sequence and not a resulting mutated sequence (according to the data in figure 1). However, page 5, line 17 teaches that the sequence GUAU is found in nucleotides 1-4 of stem-loop Ia, which is one of the regions mutated in the claim. It is not clear whether stem-loop Ia is mutated or not, or alternatively, what region within loop Ia is mutated. This rejection affects all dependent claims.

Claim 19 is vague and indefinite because it cannot be discerned what is intended or encompassed by "a part thereof".

Claim 20 is also vague and indefinite because it cannot be determined which "part of stem loop Ib" is deleted.

Claim 21 states that the nucleotide sequences at the 5'end of the genome is 5'-GUAUAU or 5'-GUAUCCU. However, the sequence alignment of various pestiviruses in figure 1 teaches that the conserved 5' genome sequence is: GUAUACG. Therefore, is the claim referring to the naturally occurring sequence or the 5'sequence after it has been mutated?

Claim 22 states that the loop portion of stem Ib contains adenosine residues, "if present". The pestivirus mutant of claim 15 may have mutations in one or both stem loops and it is presumed that neither stem loop is absent before recombinant alteration. Is stem loop Ib only transiently present in pestiviruses?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 and 35-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to an attenuated pestivirus mutant comprising one or more mutations one or both of the stem loops Ia and Ib of the 5' NTR region of the pestivirus genome. The 5' end of the genome comprises the nucleotide sequence –GUAU. As discussed above, it cannot be determined whether the Ia stem-loop is actually mutated or what portion of the loop can be altered since this 5' N-terminal sequence is the first 4 nucleotides of the Ia stem-loop. In addition, the claims encompass a wide range of pestivirus mutants that comprise a single mutation in either stem-loops Ia or Ib, as well as mutations comprising both loops. The specification does not teach a pestivirus mutant that has a single point mutation in either stem-loop that is also attenuated, nor does the specification teach an attenuated pestivirus mutant that has both stem-loops completely deleted. There is also insufficient guidance for determining which mutation(s) will result in an attenuated mutant. Therefore, since the claims encompass a

genus comprising a wide variety of possible mutants of each pestivirus, the specification does not reasonably convey possession of these undefined pestivirus mutants.

Claims 1-24 and 35-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an attenuated pestivirus mutant comprising at least one mutation in one or both of the stem loops Ia and Ib of the 5' NTR region of any pestivirus genome, where the 5' N-terminus comprises the nucleotide sequence –GUAU. As discussed above, it cannot be determined what portion of the stem-loop Ia is mutated since this 5' N-terminal sequence is the first 4 nucleotides of the Ia stem-loop. Further, the disclosure does not convey possession of all possible mutations within the genus that will result in an attenuated pestivirus.

The working examples are limited to strain C7 of the BVDV-1 virus. Although Figure 1 of the disclosure, Becher et al. (Journal of Virology. 1998; 72 (6): 5165-5173), and Frolov et al. (RNA. 1998; 4: 1418-1435) teach that the 5' N-terminal sequence is GUAU is conserved, the skilled artisan would doubt that every pestivirus could be altered in the same way to yield a weakened virus since there exists a multitude of variation between the different pestiviruses. The specification teaches that the pestiviruses have 60-70% sequence homology between the genomes. Therefore, the genomes are distinct from each other by a third to almost half of their genomes. Further, the working examples of the disclosure indicate diverse phenotypes between clones of the same strain of BVDV. The inventors teach on page 8, line 34 to page 9, line 10, that the 5' end sequence was determined for BVDV-1 CP7 strain and sequence comparison with

other BVDV-1 strains (NADL and Osloss) at the 5'end exhibited "marked variation" between the sequences of the different strains. On page 10, lines 15-22, CP7 cDNA clones, 9, 20, and 26 comprising the authentic 5'end sequence serially passaged in MDBK cells resulted in a number of genetically unstable mutants. One mutant BVDV-1 CP7-5A with 5 alanine residues following position 44 resulted in recovery of infectious virus and is genetically stable. Other clones were not determined to be genetically stable. The specification fails to teach a pattern for which mutations in which regions of every pestivirus will result in an attenuated strain and the skilled artisan would not be able to distinguish between an attenuating mutation and an unfavorable one. The inventors conclude that if the entire step-loop Ib is deleted, replication is lost and that the Ib loop portion containing 5 adenosines are necessary to have a genetically stable BVDV. However, it has not been demonstrated that this site is required for all other pestiviruses. Also, the skilled artisan would doubt that identical manipulation of different strains and diverse viruses would yield the same successful phenotype.

The working examples also do not demonstrate predictable methods for which nucleotide mutations lead to attenuation. The inventors conclude that stem-loops Ia and Ib can be altered in any way as long as the 5' sequence GUAU is present for replication ability. In general, this rule seems to apply in analyzing the various clones of BVDV-1 CP7. However, this is not always the case since SL-8 and Δ 2-31 comprising deletions in the required 5' sequence were found to be genetically stable and lesser infectivity from the wild-type clone. This inconsistency between genotypic sequence characteristics and phenotypic observations between clones of one BVDV strain only adds to the lack of assurance for manipulating other strains of BVDV-1, much less other pestiviruses.

There is also contradiction in the art for whether the instantly claimed phenotypes lead to attenuated mutants. The specification and Becher et al. teach that if the entire stem-loop structures Ia and Ib are deleted, replication is severely reduced, even in the presence of 5'-GUAU. However, Frolov et al. teaches that BVDV chimeras lacking the stem-loop structures while retaining GUAU were not detrimentally affected in replication capacity. Therefore, there is a contradiction in the art and the instant teachings in the specification that lends further proof of the unpredictable nature of how and where to attenuate these pestivirus mutants.

Although data in the specification demonstrates lower infectivity and reduced replicative ability in some clones, there is no data concerning the level of attenuation with the desired protective response. There is no administration of the clones in the working examples to pestivirus-infected animals and no experimental data drawn to administering the clones and further challenging the animals. The inventors conclude that the clones are "expected to be attenuated" on page 13, line 32. However, this conclusion is insufficient to alleviate concerns in the art regarding whether the pestivirus mutants disclosed are safe for administration. The specification clearly states on page 2, lines 9-11, that "it is still not known which region(s) of the genome should and can be modified to lead to a safe and effective vaccine strain."

Thiel et al. (" Pestiviruses", Fields Virology, 3rd edition. 1996. Lippencott-Raven, Philadelphia: 1059-1073) teaches that the amount of antigenic diversity between BVDV and BDV "sheds doubt on the prospects of effectively controlling" infection by vaccination. Thiel et al. also teaches concerns regarding duration of immunity and resistance to challenge after vaccination with attenuated viruses needs to be further investigated. See Figure 1 on page 1061

showing antigenic relationships of the pestiviruses and "Prevention and Control" section on pages 1068-1069.

There is no data provided by the inventors with respect to whether the instant composition can be administered safely without detrimental side-effects. There is no way to determine if the instant composition has long-term efficacy, what type of immune response will be elicited, or whether the composition would be effective in treating or preventing any pestivirus infection. Grooms et al. (Journal of Veterinary Diagnostic Investigation. 1998; 10 (2): 130-134, abstract only.) discusses the state of the BVDV vaccine art and the safety concerns for administering modified live vaccines due to a lack of knowledge in regarding tissue tropism and potential for causing pathology. Grooms et al. teaches isolating cytopathic BVDV from ovaries of cows after immunizing with a modified live virus. There is no teaching in the specification that alleviates these concerns in the art.

Therefore, due to the broad genus of possible mutations in any pestivirus, the lack of guidance provided by the inventor for which mutations result in an attenuating phenotype in every pestivirus, contradictions in the art regarding which mutations are necessary, the amount of variation between pestiviruses, the lack of predictability in the vaccine art for which mutations lead to attenuation without causing detrimental effects, and the lack of working examples demonstrating that the instant mutations attenuate other pestiviruses, it is determined that an undue quantity of experimentation would be required to make and use the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SAF
Shanon Foley/SAF
May 9, 2002

James C. Housel
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